Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

Timothy R. Franson, M.D., F.A.C.P.
Vice President
317.277.1324
Fax: 317.276.9960

April 23, 1998

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
HFD-001 - Bldg. WOC2, Room 6027
Woodmont Bldg. No. II
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852-1448

Dear Dr. Woodcock:

On behalf of the PhRMA/BIO working group on Abbreviated reports, I am transmitting comments regarding Section 118 (Data Requirements for Drugs & Biologics) of the FDA Modernization Act (FDAMA) of 1997 for your consideration. It is our understanding that you are the lead party designated by FDA for coordination of Sect. 118 implementation, and also the individual to whom commentary should be directed.

Reference is made to FDA-industry work group activities relating to this topic which addressed areas of mutual interest and concern prior to passage of FDAMA. For your reference, we have appended correspondence from March 17, 1997 and April 21, 1997 which are representative of our group's concerns, and which we continue to endorse.

Please also note the following additional material relating to PhRMA/BIO work group members advisement:

1. Definition of elements to be included as qualifying for abbreviated reports should include, but may not be limited to:
    - Studies conducted which will not serve as the basis for label claims, such as failed studies, abandoned indications, and similar trials, which may be further defined as:

        Studies for which statistical efficacy was not achieved, which could be determined by a host of factors including, but not limited to: failure to reach appropriate p-value; failure to determine appropriate endpoint; failure to validate surrogate endpoint; failure to enroll adequate numbers of patients for statistical power; abandoned studies; studies stopped at interim analysis due to failure to reach statistical efficacy or for other reasons; studies using inappropriate doses or routes of administration; studies stopped due to lack of clinical trial material; studies stopped due to serious adverse events.

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- Selected sections of "pivotal" studies (those trials upon which label claims will be based) used for other indications or purposes, defined as:

  studies which were successful and intended for use for a labeling indication, but which do not now support the indication in the submitted application (they may be submitted in full in a future application); studies which support the indication, but which are not used to demonstrate efficacy in the proposed label submitted in the application. If the study is used in the Integrated Summary of Efficacy in the application to FDA, or is used to demonstrate confirmatory evidence, as described in Section 115 of FDAMA, then full clinical study reports should be submitted.

In enacting Section 118, Congress provided guidance on the kinds of information suitable for abbreviated reports:

> "The Committee intends that studies that are pivotal in supporting label claims must be provided to the FDA in sufficient detail for agency reviewers to properly evaluate the study. Other information should be submitted in abbreviated or summary form." H.R. Rep. No. 105-310, at 70 (1997).

We believe that the preceding recommendations in this text are consistent with both Congressional intent and with previous discussions of our joint working group last year.

2. Agreement on common format and elements (in concept) for Sec. 118 provisions consistent with ICH-E3 synopsis: Our group advises that every element of the synopsis described in E-3 should be submitted for all study reports. For example, in the case of a failed study, synopsis would provide the medical reviewer with the explanation as to why the study failed to reach statistical efficacy. In the clinical study report itself, information is provided to include enough information about the design and execution of the study for reviewers to 1) determine the outcome of the study; 2) interpret the study safety data; 3) understand the reason(s) the study cannot be used to support effectiveness and related labeling claims; 4) determine whether the reviewers need more information; and 5) in the case of early studies, how the data should be interpreted. From the Table of Contents of E-3, we believe an abbreviated report should include the E3 synopsis, and could include several or more of the following elements, depending on the type & nature of study:

1. Title Page
3. Table of Contents for the Individual Clinical Study Report
8. Study Objectives
9. Overall Study Design and Plan: Description
9.5 Efficacy and Safety Variables
12 Safety Evaluation
13 Discussion and Overall Conclusions
14.1 Demographic Data Summary figures and tables
14.3 Safety Data Summary figures and tables
16.2 Patient Data Listings (Safety)
16.3 Case Report Forms (NB further definition of criteria under which such detailed information be required must be judiciously constructed and further discussed).

Please also note that our work group is of the opinion that Sect. 16.4 should not be included.

3. Modification of electronic submission draft guidance (April 6, 1998) consistent with ideal elements for abbreviated report format as in the preceding item: The guidance on "Providing Regulatory Submissions in Electronic Format - NDAs" should be revised to accommodate abbreviated reporting. Specifics on what electronic case report tabulations (Appendix 16.2) are needed and the alternative datasets should be clear and consistent with the recommendation on abbreviated reporting.
4. Processes to assure compliance & consistency across agency offices and divisions should be promulgated, as well as processes for sponsors to seek acceptable deviation from guidance requirements. Furthermore, all preceding understandings should be integrated into the discussion of ICH common technical document (ICH-M4) including where possible modular approaches.

You can be assured that the industry working group remains committed to appropriate and thorough safety assessments. Please contact me if there are any questions regarding the material in the preceding text, or of related concerns. We appreciate the opportunity to offer commentary regarding this important progress.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D.
Vice President
Clinical Research and
Regulatory Affairs - U.S.

TRF/saa

Enc.

cc: PhRMA/BIO Working Group:
Russ Bantham
Janice Bush
Tom Copmann
Alan Goldhammer
Bill Kennedy
John Siegfried
Laurie Smaldone
Matt Van Hook
Larry Versteegh

Jane Axelrad
Associate Director for Policy
CDER

Lilly

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

Timothy R. Franson, M.D., F.A.C.P
Executive Director
(317) 277-1324
Facsimile (317) 277-1697

March 17, 1997

via FAX

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
HFD-001 - Bldg. WOC2, Room 6027
Woodmont Bldg. No. II
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852-1448

Dear Dr. Woodcock:

On behalf of the PhRMA/BIO members of the Clinical Issues Working Group, I am providing the following comments to the March 5, 1997 draft revision of FDA's position paper relating to "Summary Data Issues". It is noted that this material has been previously discussed in our industry-FDA working group, and that this draft does indeed reflect the spirit and intent of the prior reviews.

Regarding "Statement of Problem #1", the draft does capture the content of proposed changes consistent with our working group's consensus. There is one process comment, that being on "approach to Problem #1" - Item 2.c. - it is suggested that this section be divided into two separate points (i.e., current 2.c. mentions abbreviated efficacy reports, and also safety guidance which may be better addressed independently). We also desire clarification as to whether "abbreviated submissions" cited in 2.a. differ in content from "studies...synopsis form" mentioned in 2.b. (i.e., whether this synopsis is a type of abbreviated submission for clinical pharmacology studies or instead a distinct category).

Regarding "Statement of Problem #2", we would appreciate clarification of Point 1 under "approach to Problem #2", in order to define whether the proposed efficacy summary is seen as incremental to what is currently provided in conventional NDA summaries. If not, we agree with the content, with this clarification. If, however, it is incremental/new, we would like to further discuss how reviewers might utilize such a compilation, and whether this change would be consistent with the intent of the ICH Core Technical Document initiative.

We agree with the conclusion of this position paper, support the opportunity to cooperate in guidance development for summary data recommendations, and concur that the resolution of this issue is best pursued via guidance development. We also applaud the

agency's initiative and willingness to pursue innovative improvements which expedite NDA efficacy review processes without compromise of our shared interests in safety assurances.

Please contact me should there be any questions regarding this material. Thank you for the opportunity to interact in this process.

Sincerely,

ELI LILLY AND COMPANY

Tim Franson

Timothy R. Franson, M.D.
Executive Director
Regulatory Affairs
(co-chair, FDA/Industry Clinical
Issues Working Group)

TRF/saa

cc: Dr. A. Goldhammer (via FAX)
Dr. W. Kennedy (via FAX)
Dr. R. Orzolek (via FAX)
Dr. J. Siegfried (via FAX)

April 21, 1997

DRAFT

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
HFD-001 - Bldg. WOC2, Room 6027
Woodmont Bldg. No. II
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852-1448

Dear Dr. Woodcock:

In response to your March 28, 1997 memo regarding "Efficacy Data Requirements", which included the edits from Dr. Temple, please note the following comments, which represent the opinions of industry participants involved in our Clinical Issues Working Group:

1. Statement of Problem #1 - we agree with the edited version, with no further revisions to offer

2. Approach to Problem #1 - we agree with all changes in the edited version, except the deletion of C.(3) citation of studies not to be relied upon for labeling claims; it would be prudent to specifically state this point, which frames the intended use of data, and we propose reinserting that language (attached)

3. Statement of Problem #2 - we agree with the edited version

4. Approach to Problem #2 - we should assure that there are more explicit agreements as to the scope of additional data requests, lest this section be interpreted as requiring sponsors to provide data summaries beyond current requirements

DRAFT

We continue to share your commitment to comprehensive safety assessments for all drug and biological products in the interest of public health and scientific rigor.

Please contact me should there be any questions regarding this material. We look forward to working with you and your agency colleagues to develop the two guidances proposed in this position paper, in order to achieve a shared goal of streamlining efficacy reports without compromising data quality. Thank you for the opportunity to review this document.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D.
Executive Director
Regulatory Affairs

TRF/saa

Enc.

c. Each guidance will contain one or more model abbreviated report formats for various categories of studies. These abbreviated report formats will ~~be designed to enable FDA~~ include enough information about the design and execution of the study for reviewers to ~~determine~~:

(1) know the outcome of the study;

(~~1~~ 2 ~~facts about the design and execution of the study needed to~~ interpret the study safety data;

(~~2~~3) ~~in the case of abbreviated efficacy studies, the reasons the study results would not be relied upon in labeling,~~ if not obvious, understand the reason(s) the study cannot be used to support effectiveness, labeling claims and related

(4), determine whether they need more information;

(~~3~~5) this is not at all clear In the case of certain early studies, how the data should be interpreted.

3. FDA will carry out a small study to see what proportion of current filings could be eliminated by abbreviated reports.

4. FDA will explore mechanisms under which certain high page volume, low information content submissions, such as CV's,

March 27, 1997

EFFICACY DATA REQUIREMENTS

This topic refers to efficacy data submitted in marketing applications. All parties agree that safety data is not included. Two related problems related to efficacy data have been identified by the industry representatives.

Statement of Problem #1

One identified problem is that excessive or unnecessary efficacy information is being submitted in the form of detailed reports for studies where that level of detail is not required to make a regulatory decision or for product labeling. This requires extra preparation time on the part of industry and may result in unnecessary effort being expended by FDA reviewers. It is not clear if this information is submitted at the request of FDA staff, or if sponsors are simply filing it, or both. All parties agree that the best solution to this problem is an up-front agreement between the sponsor and the FDA on what data should be filed. However, since mechanisms to achieve ~~this~~ such agreement are already in place, i.e., pre-PLA or pre-NDA meetings, ~~and~~ and there is explicit recognition in the clin/stat guideline and ICH E-3 of ~~the appropriateness of~~ abbreviated reports, yet filing of unneeded material is still occurring, it is clear that additional efforts should be made to clarify ~~what~~ the types of information that ordinarily can be submitted in abbreviated form. ~~only.~~

Approach to Problem #1

1. All parties will make strong efforts to reach agreement at pre-filing meetings on what efficacy information can be filed in abbreviated form for a particular application.

2. FDA will develop two guidance documents (one for early studies and one for ~~formal efficacy~~ later trials) ~~which~~ that will provide the following information.

   a. The kinds of ~~efficacy~~ studies (e.g., uncontrolled studies, controlled studies that failed to distinguish drug from placebo, studies that were terminated, studies of poor quality, studies of uses not submitted for ~~approval~~ in the application, or active control equivalence studies without placebo that (in U.S.) would not be considered for evidence of effectiveness) that should be considered for abbreviated ~~submissions~~ reports. "Abbreviated ~~submissions~~ reports" are ~~defined as submissions~~ reports with much less detail of study design and results and without case report tabulations of the efficacy data.

   b. The kinds of early clinical studies, e.g., certain clinical pharmacology studies, that could be submitted in an abbreviated form accompanied by data tabulations.

c. Each guidance will contain one or more model abbreviated report formats for various categories of studies. These abbreviated report formats will ~~be designed to enable FDA~~ include enough information about the design and execution of the ~~study~~ for reviewers to ~~determine~~:

(1) know the outcome of the study;

(~~1~~ 2 ~~Facts about the design and execution of the study needed to~~ interpret the study safety data;

(~~23~~) ~~In the case of abbreviated efficacy studies, the reasons the study results would not be relied upon in labeling;~~ if not obvious, understand the reason(s) the study cannot be used to support effectiveness; and related labeling claims

(4), ~~determine~~ whether they need more information;

(~~35~~) ~~this~~ is not ~~at~~ all clear In the case of certain early studies, how the data should be interpreted.

3. FDA will carry out a small study to see what proportion of current filings could be eliminated by abbreviated reports.

4. FDA will explore mechanisms under which certain high page volume, low information content submissions, such as CV's,

could be abbreviated, eliminated, held back, or summarized (ICH-E3 already permits this for very large studies with numerous investigators).

5. Time line for Guidance Issuance

   a. FDA will issue draft guidances for comment by the end of FY 1997.

   b. FDA will issue final guidance by the end of CY 1997.

Statement of Problem #2

Industry representatives maintain that some FDA review staff spend too much time and effort reanalyzing primary efficacy data and doing exploratory analyses of these data. Therefore, it is suggested that they evaluate summaries of the effectiveness data and simply spot check or audit the primary data for accuracy, etc.

FDA representatives ~~pointed out that the Agency adds value to the process through its~~ did not accept the view that FDA should simply accept analyses as provided and argued the value of independent scientific review and ~~that this is an extremely important function~~ a review that cannot be condensed with summarized data. FDA representatives ~~also feel~~ felt that ~~the issue of reviewers doing excessive analyses or misinterpreting analyses is a management problem that must be solved internally~~ a sponsor who felt a reviewer was making excessive or unreasonable demands for further

data or analyses needed to appeal to the reviewer's supervisor. FDA and industry representatives agree, however, that, as indicated in ~~regulations~~, once the extent of data filing has been agreed upon, reviewers desiring ~~additional~~ more extensive data submissions should have to go through the supervisory chain to make such a request. This would not limit the ability of the reviewer to seek further information to respond to questions that arise in the course of review.

Approach to Problem #2

It is likely that the parties can come to some agreement on procedures for requests for additional data. FDA agrees to develop and implement such a procedure by the end of FY 1997.

Needs discussion. Real doubt that this is a serious issue.

Conclusion

The working group believes that substantial progress can be made in ~~abbreviating the amount of efficacy reports and data currently filed~~ decreasing the number of complete reports and the size of filings in marketing applications ~~and efficacy supplements~~ by utilizing abbreviated reports where appropriate.

R. Temple's revisions

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